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Synthesis of Coumarins, 4-Hydroxycoumarins, and 4-Hydroxyquinolinones by Tellurium-Triggered Cyclizations[1]

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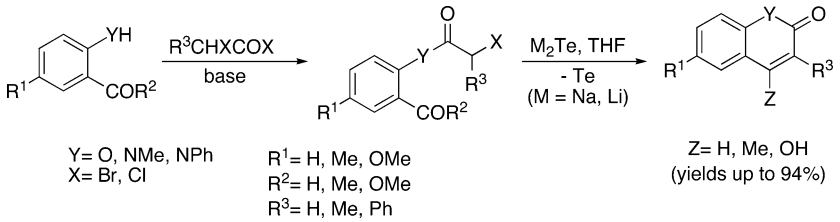

Coumarins, 4-hydroxycoumarins, and 4-hydroxyquinolin-2(1*H*)-ones can be conveniently prepared by treatment of α-halocarboxylic acid esters of salicylaldehyde, *o*-hydroxyacetophenone, methyl salicylate, and methyl *N*-methyl- or *N*-phenylanthranilates with sodium or lithium telluride. Phenylketene formation competes with cyclization of the α-chlorophenylacetate ester of methyl salicylate as demonstrated by a trapping experiment with benzylamine. Elemental tellurium may be recovered and reused.

Introduction

Coumarins are important compounds found widely in nature[2] and have numerous applications in medicine (e.g. anticlotting)[3] and perfumery,[4] as dyes in laser technology,[5a] and as fluorescent indicators.[5b] Certain coumarins inhibit acetylcholinesterase (involved in Alzheimer's disease),[6] aromatase (breast cancer therapy),[7] and squalene-hopene cyclase (cholesterol lowering and antitrypanosomal drugs).[8] They also show anti-HIV,[9] antifungal,[10] and anti-cancer[11] activity. Compounds derived from 4-hydroxycoumarin protect liver cells from damage by peroxides.[12]

4-Hydroxyquinolin-2(1*H*)-ones have been investigated as NMDA (*N*-methyl-D-aspartate)[13] and serotonin 5-HT_3 [14] receptor antagonists, the former being useful in allowing drugs to cross the blood−brain barrier and the latter of use in controlling vomiting induced by cancer chemotherapy. In addition, they are intermediates in alkaloid synthesis.[15]

The classic Reformatsky reaction[16−19] has been improved recently by the use of samarium,[20−23] indium,[24] rhodium (catalytic)−diethyl zinc,[25] chromium,[26,27] titanocene,[28] and ultrasound.[29] Investigations of analogues

(1) Preliminary report: Dittmer, D. C.; Li, Q. *Abstracts of Papers*; 228th National Meeting of the American Chemical Society, Philadelphia, PA; American Chemical Society: Washington, DC, 2004; ORGN 639.

(2) Murray, R. D. H. *Prog. Chem. Org. Nat. Prod.* **2002**, *83*, 1−673 and references therein.

(3) (a) *Coumarins*: *Biology*, *Applications*, *and Mode of Action*; O'Kennedy, R., Thomas, R. D., Eds.; Wiley: Chichester, UK, 1997. (b) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev.* **2003**, *23*, 322−345. (c) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins*; Wiley: Chichester, UK, 1982.

(4) Clark, G. S. *Perfum. Flavor.* **1995**, *20*, 23−34.

(5) (a) Sekar, N. *Colourage* **2003**, *50*, 55−56. (b) Brun, M.-P.; Bischoff, L.; Garbay, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3432−3436.

(6) Rollinger, J. M.; Hornick, A.; Langer, T.; Stuppner, H.; Prast, H. *J. Med. Chem.* **2004**, *47*, 6248−6254.

(7) Chen, S.; Cho, M.; Karlsberg, K.; Zhou, D.; Yuan, Y.-C. *J. Biol. Chem.* **2004**, *279*, 48071−48078.

(8) Cravotto, G.; Balliano, G.; Robaldo, B.; Oliaro-Bosso, S.; Chimichi, S.; Boccalini, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1931−1934.

(9) (a) Hariprassad, V.; Talele, T. T.; Kulkarni, V. M. *Pharm. Pharmacol. Commun.* **1998**, *4*, 365−372. (b) Kaye, P. T.; Musa, M. A.; Nichinda, A. T.; Nocanda, X. W. *Synth. Commun.* **2004**, *34*, 2575−2589.

(10) Sardari, S.; Nishibe, S.; Daneshtalab, M. *Stud. Nat. Prod. Chem.* **2000**, *23*, 335−393.

(11) Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des.* **2004**, *10*, 3797−3811.

(12) Refouvelet, B.; Guyon, C.; Jacquot, Y.; Girard, C.; Fein, H.; Bévalot, F.; Robert, J.-F.; Heyd, B.; Mantion, G.; Richert, L.; Xicluna, A. *Eur. J. Med. Chem.* **2004**, *39*, 931−937.

(13) (a) Rowley, M.; Kulagowski, J. J.; Watt, A. P.; Rathbone, D.; Stevenson, G. I.; Carling, R. W.; Baker, R.; Marshall, G. R.; Kemp, J. A.; Foster, A. C.; Grimwood, S.; Hargreaves, R.; Hurley, C.; Saywell, K. L.; Tricklebank, M. D.; Leeson, P. D. *J. Med. Chem.* **1997**, *40*, 4053−4068. (b) Zhou, Z.-L.; Navratil, J. M.; Cai, S. X.; Whittemore, E. R.; Espitia, S. A.; Hawkinson, J. E.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *Bioorg. Med. Chem.* **2001**, *9*, 2061−2071.

(14) Hayashi, H.; Miwa, Y.; Ichikawa, S.; Yoda, N.; Miki, I.; Ishii, A.; Kono, M.; Yasuzawa, T.; Suzuki, F. *J. Med. Chem.* **1993**, *36*, 617−626.

(15) (a) Watters, W. H.; Ramachandran, V. N. *J. Chem. Res. Synop.* **1997**, 184−185. (b) Majumdar, K. C.; Choudhury, P. K. *Synth. Commun.* **1993**, *23*, 1087−1100. (c) Grundon, M. F.; Ramachandran, V. N. *Tetrahedron Lett.* **1985**, *26*, 4253−4256. (d) Corral, R. A.; Orazi, O. O.; Autino, J. C. *Tetrahedron Lett.* **1983**, *24*, 2359−2360. (e) Reisch, J.; Mueller, M.; Mester, I. *Z. Naturforsch. B*: *Anorg. Chem., Org. Chem.* **1981**, *36B*, 1176−1179.

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of the Reformatsky reaction by treatment of α-halocarbonyl and related compounds with tellurides usually resulted in the protonation of the enolate or the elimination of ketene;[30] but intermolecular reactions with aldehydes[31] and ketones[32] have been observed. Cyclopropanalogues of α-haloketones undergo similar reactions with telluride ions.[33] An initial attempt to prepare coumarin by intramolecular cyclization of the bromoacetate ester of salicylaldehyde triggered by sodium telluride failed.[30g] No other telluride-induced attempted cyclization appears to have been reported.

Coumarins (2*H*-1-benzopyran-2-ones) have been prepared by a number of methods involving formation of a 3−4 carbon−carbon bond.[34] For example, the Kostanecki−Robinson reaction of *o*-hydroxyarylalkyl ketones with an acid anhydride and the sodium salt of an acid produces coumarins by formation of the 3−4 carbon−carbon bond via the ester enolate, but chromones (4*H*-1-benzopyran-4-ones) can be the major products via the ketone enolate, and yields can be variable.[35,36] A method (Claisen) that avoids the chromone byproducts of the Kostanecki−Robinson reaction is the treatment of methyl esters of 2-alkanoyloxybenzoic acids with metallic sodium[37a,b] or with bases.[37c−f] Coumarins also have been prepared in good yields by a ring-closing metathesis reaction (3−4 bond formation),[38] but this reaction is not ideal with respect to carbon atom economy and requires a ruthenium catalyst.

SCHEME 1. Synthesis of Coumarins

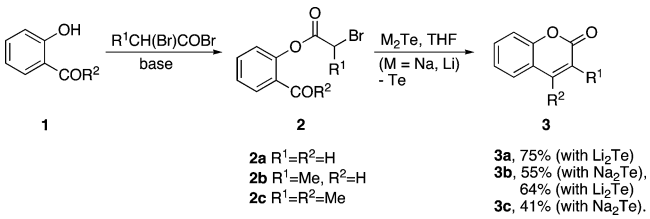


TABLE 1. Solvent Effects on Yields of Coumarin 3a via Sodium or Lithium Telluride

entry	solvent	*T*, °C	time, h	telluride	coumarin, %
1	DMF	−20 to rt	2	Na_2Te	trace[a]
2	THF	−20 to rt	16	Na_2Te	11−23
3	benzene−THF (19:1)	6 to rt	16	Na_2Te	46
4	ether−THF (9:1)	−20 to rt	24	Na_2Te	45
5	THF	−78 to rt[b]	1.5	Li_2Te	75

[a] Reference 30g: salicylaldehyde, 8%; salicylaldehyde dimeric acetal, 32%. This result is explained by the authors via presumed ketene formation. [b] Allowing the reaction in THF to proceed at −78 °C for 1 h with quick warming (5−10 min) to room temperature and further standing for 30 min gave the best results.

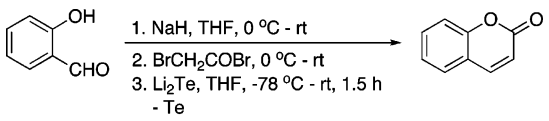
Results and Discussion

Synthesis of Coumarins and 4-Hydroxycoumarins. We have achieved the previously unsuccessful sodium telluride-triggered cyclization of the bromoacetate of salicylaldehyde to coumarin (yields 11−75%) (Table 1). The cyclization proceeds by formation of the phenolate ester enolate, elemental tellurium, and bromide ion. The enolate anion either attacks the ortho carbonyl group leading to cyclization or eliminates a phenolate ion to give a ketene.

The yield of coumarin depends on reaction conditions and the workup. When sodium telluride is the reagent, the yield is improved by use of solvents (THF, ether−THF, benzene−THF) less polar than the DMF of the earlier failed attempt[30g] (Table 1, entries 1−4).

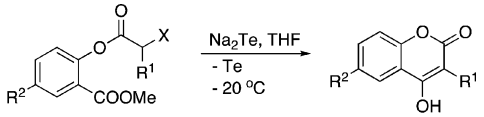
(16) Fürstner, A. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999; pp 287−305.
(17) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648.
(18) Fürstner, A. *Synthesis* **1989**, 571−590.
(19) Rathke, M. W. *Org. React.* **1975**, *22*, 423−460.
(20) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.
(21) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889−3890.
(22) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556.
(23) For a review see: Banik, B. K. *Eur. J. Org. Chem.* **2002**, 2431−2444.
(24) For reviews see: (a) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633−655. (b) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959−1982.
(25) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551.
(26) (a) Dubois, J. E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* **1985**, *26*, 4371−4372. (b) Hojo, M.; Sakata, K.; Ushioda, N.; Watanabe, T.; Nishikori, H.; Hosomi, A. *Organometallics* **2001**, *20*, 5014−5016.
(27) For a review see: Fürstner, A. *Chem. Rev.* (*Washington*, *D.C.*) **1999**, *99*, 991−1045.
(28) Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615−3617.
(29) (a) Ross, N. A.; MacGregor, R. R.; Bartsch, R. A. *Tetrahedron* **2004**, *60*, 2035−2041. (b) Ross, N. A.; Bartsch, R. A. *J. Org. Chem.* **2003**, *68*, 360−366.
(30) (a) Bergson, G. *Acta Chem. Scand.* **1957**, *11*, 571−572. (b) Engman, L.; Cava, M. P. *J. Org. Chem.* **1982**, *47*, 3946−3949. (c) Clive, D. L. J.; Beaulieu, P. L. *J. Org. Chem.* **1982**, *47*, 1124−1126. (d) Osuka, A.; Suzuki, H. *Chem. Lett.* **1983**, 119−120. (e) Engman, L. *Organometallics* **1986**, *5*, 427−437. (f) Huang, Z.; Xia, L.; Huang, X. *Synth. Commun.* **1988**, *18*, 1167−1170. (g) Padmanabhan, S.; Ogawa, T.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2114−2116. (h) Li, C. J.; Harpp, D. N. *Tetrahedron Lett.* **1990**, *31*, 6291−6294. (i) Vasil'ev, A. A.; Engman, L. *J. Org. Chem.* **1998**, *63*, 3911−3917. (j) Suzuki, H.; Padmanabhan, S.; Ogawa, T. *Chem. Lett.* **1989**, 1017−1020. (k) Huang, X.; Jiang, L. M. *Chin. Chem. Lett.* **1993**, *4*, 315−316.
(31) (a) Suzuki, H.; Inouye, M. *Chem. Lett.* **1986**, 403−406. (b) Huang, X.; Xie, L.; Wu, H. *Tetrahedron Lett.* **1987**, *28*, 801−802. (c) Suzuki, H.; Manabe, H.; Inouye, M. *Nippon Kagaku Kaishi* **1987**, 1485−1489. *Chem. Abstr.* **1988**, *108*, 167071. (d) Matsuki, T.; Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2105−2107. (e) Zhou, Z.-L.; Shi, L.-L.; Huang, Y.-Z. *Synth. Commun.* **1991**, *21*, 1027−1037.
(32) Fukuzawa, S.; Katsuhiko, H. *J. Chem. Soc.*, *Perkin Trans. 1* **1993**, 1963−1965.
(33) Avilov, D. V.; Malusare, M. G.; Arslancan. E.; Dittmer, D. C. *Org. Lett.* **2004**, *6*, 2225−2228.
(34) Williams, A. C.; Camp, N. In *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations*; Bellus, D., Ley, S. V., Noyori, R., Regitz, M., Schaumann, E., Shinkai, E., Thomas, E. J., Trost, B. M., Reider, P. J., Series Editors; Thomas, E. J., Volume Editor; Thieme: Stuttgart, Germany, 2004; Vol. 14, pp 347−438.
(35) (a) Kostanecki, S.; Rózycki, A. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 102−112. (b) Baker, W.; Robinson, R. *J. Chem. Soc.* **1925**, *127*, 1981−1986. (c) Baker, W.; Eastwood, F. M. *J. Chem. Soc.* **1929**, 2897−2907. (d) Heilbron, I. M.; Hey, D. H.; Lythgoe, B. *J. Chem. Soc.* **1936**, 295−300. (e) Neelakantan, S.; Raman, P. V.; Tinabaye, A. *Indian J. Chem. Sect. B*: *Org. Chem. Incl. Med. Chem.* **1982**, *21B*, 256−257.
(36) For example, cyclizations of *o*-hydroxyacetophenone and monoethyl esters of dicarboxylic acids with DBU as base gave coumarins in yields of 1−4% and chromones in yields of 6−20%: Yamaguchi, S.; Saitoh, M.; Kawase, Y. *J. Heterocycl. Chem.* **1991**, *28*, 125−127.
(37) (a) Mentzer, C.; Meunier, P. *Bull. Soc. Chim. Fr.* **1943**, *10*, 356−361. (b) Stahmann, M. A.; Wolff, I.; Link, K. P. *J. Am. Chem. Soc.* **1943**, *65*, 2285−2287. (c) Silverman, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 3910−3915. (d) Gandhidasan, R.; Neelakantan, S.; Raman, P. V.; Sripathi, S. K. *Indian J. Chem.*, *Sect. B*: *Org. Chem. Incl. Med. Chem.* **1988**, *27B*, 849. (e) Lokhande, P. D.; Ghiya, B. J. *J. Indian Chem. Soc.* **1989**, *66*, 314−315. (f) Da Re, P.; Sandri, E. *Chem. Ber.* **1960**, *93*, 1085−1088.
(38) (a) Chatterjee, A. K.; Toste, F. D.; Goldberg, S. D.; Grubbs, R. H. *Pure Appl. Chem.* **2003**, *75*, 421−425. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.

SCHEME 2. One-Pot Synthesis of Coumarin



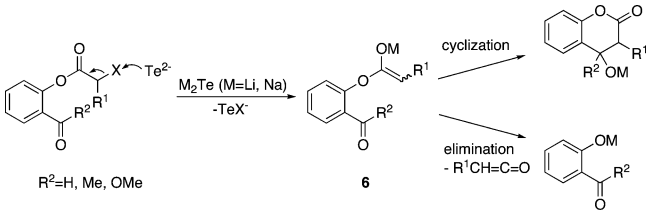
1a **3a**, 55%

SCHEME 3. Synthesis of 4-Hydroxycoumarins



4a X=Br, R^1=Me, R^2=H — **5a**, 54%
4b X=Br, R^1=R^2=Me — **5b**, 94%
4c X=Br, R^1=Me, R^2=OMe — **5c**, 67%
4d X=Cl, R^1=Ph, R^2=H — **5d**, 10%

SCHEME 4. Telluride-Triggered Enolate Formation

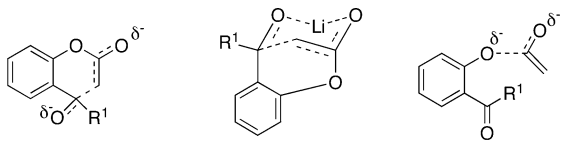


R^2=H, Me, OMe **6**

A change of the telluride counterion from sodium to lithium reduced reaction times and increased the yield of coumarin to 75% (Table 1, entry 5). The α-bromopropionate of salicylaldehyde and of *o*-hydroxyacetophenone also gave the expected coumarins in 41−64% yields (Scheme 1). A convenient one-pot procedure gave coumarin in an overall yield of 55% (Scheme 2). Salicylic acid derivatives **4a**−**d** gave 4-hydroxycoumarins **5a**−**d** (Scheme 3).

The isolation of coumarins is improved by workup with aqueous hydrogen peroxide (30%) and sodium bicarbonate[39] to remove the triethylborane byproduct, formed in the reduction of tellurium by lithium triethylborohydride, because Lewis acids complex with coumarin.[40]

The telluride reactions are interpreted as proceeding through an ester enolate **6** formed by removal of the halide by the nucleophilic telluride ion as previously suggested (Scheme 4).[30−33] The unstable $TeBr^-$ or $TeCl^-$ ion decomposes to elemental tellurium and the halide ion. Two pathways are possible for the fate of the enolate **6**: (1) the desired Dieckmann-type cyclization to coumarins perhaps assisted by chelation with sodium or lithium cations (Figure 1, transition states **7** or **8**) or (2) elimination of a stable phenolate anion and a more or less stable ketene (Figure 1, transition state **9**). Ketene elimination from chloroacetates of phenols was suggested in the deprotection of these esters by treatment with sodium telluride in DMF[30j] or sodium hydrogen telluride in ethanol[30k] but products that would be formed from ketene were not reported. The elimination of a phenol anion is enhanced by electron-withdrawing groups.[41] One can presume elimination of ketene in the reaction of 2′-



7 **8** **9**

FIGURE 1. Possible transition states for cyclization and elimination.

bromoacetoxyacetophenone with trimethyl phosphite, which gave 2′-hydroxyacetophenone (yield not given) in addition to the 3-phosphonate of coumarin (38% yield).[42]

The extent of ketene formation in reactions of **2** and **4** with telluride ion is expected to be related to the stabilities of the ketene and the phenolate leaving group, which in turn depends on the substituents. The Hammett σ^- values for the three substituents used in this investigation, formyl, acetyl, and methoxycarbonyl, are $\sigma^-_{CHO} = 1.03$, $\sigma^-_{COMe} = 0.84$, and $\sigma^-_{COOMe} = 0.75$, respectively.[43] With the less electron-withdrawing COOMe group, yields of coumarins are generally good (**5a**−**c**, 54−94%), whereas with the more electron-withdrawing CHO and COMe groups, the roles of solvent and chelation effects (Table 1) become more significant. For example, the yield of coumarin **3a** with Na_2Te increases with the decrease in solvent polarity (Table 1, entries 1−4). The greater dispersion of negative charge in cyclization transition states **7** or **8** as compared to elimination transition state **9** is favored in less polar solvents. It is noteworthy that the classic Dieckmann cyclization is usually performed in nonpolar solvents (e.g. toluene, benzene).[44] However, the overall influence of solvent may be a more complex issue as relative solvation of the reactants, products, intermediates, and transition states has to be taken into account. The higher yield of coumarin **3a** in the reaction with Li_2Te (Table 1, entry 5) may reflect the better ability of lithium ion for chelation (transition state **8**). In the reaction of **4d**, the stability of phenylketene may account for the extensive elimination and low yield of coumarin **5d** (Scheme 3). 3-Arylcoumarins are generally expected to be formed only in low yields. To confirm the formation of phenylketene, it was trapped with benzylamine to afford amide **11** (56%) (Scheme 5).[45]

The yields of coumarins **3a**−**c** and **5a**−**d** (Schemes 1 and 3) can be compared with yields previously reported for some of these compounds prepared by methods involving formation of the 3−4 carbon−carbon bond. Yields of **3a**−**c** by the ring-closing metathesis reaction were 89%, 88%, and 45%, respectively.[38a] Coumarin **3c** was obtained from *o*-hydroxyacetophenone by reaction with a *C*-phosphonoketenimine followed by hydrolysis of

(39) Sodium bicarbonate was used as base instead of the more common sodium hydroxide (Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064−3066) to avoid possible hydrolysis of the coumarin lactone function.

(40) Lewis, F. D.; Barancyk, S. V. *J. Am. Chem. Soc.* **1989**, *111*, 8653−8661.

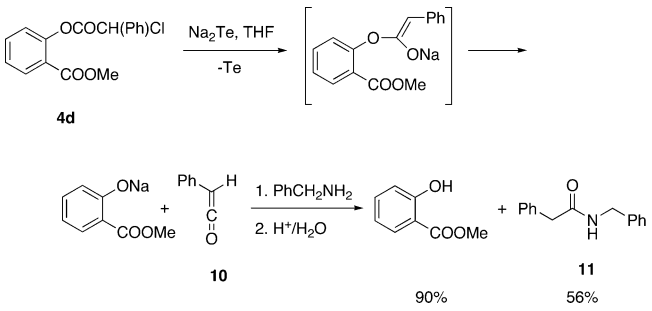
(41) (a) Ketene formation by elimination of phenolates from acetate esters substituted with α-electron-withdrawing groups has been demonstrated: Bruice, T. C.; Holmquist, B. *J. Am. Chem. Soc.* **1968**, *90*, 7136−7138. Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993−3002, 3003−3009. Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956−5964. (b) Other ketene eliminations from esters: Casanova, J., Jr.; Werner, N. D.; Kiefer, H. R. *J. Am. Chem. Soc.* **1967**, *89*, 2411−2416. Thea, S.; Cevasco, G.; Guanti, G.; Kashefi-Naini, N.; Williams, A. *J. Org. Chem.* **1985**, *50*, 1867−1872.

(42) Kostka, K.; Pastuszko, S.; Kotynski, A.; Budzisz, E. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *134/135*, 199−209.

(43) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* (*Washington, D.C.*) **1991**, *91*, 165−195.

(44) (a) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1−203. (b) Hauser, C. R.; Hudson, B. E., Jr. *Org. React.* **1949**, *1*, 266−302.

SCHEME 5. Trapping of Phenylketene

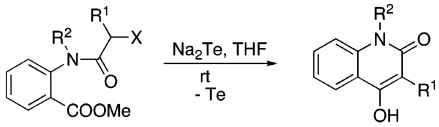


the imine product (91% yield),[46a] and via cyclization of a low-valent titanium enolate of an α-ketoester of *o*-hydroxyacetophenone (80%).[46b] Variations of the Dieckmann cyclization have been applied to the synthesis of **5a** and **5d**. Treatment of the methyl ester of 2-propionyloxybenzoic acid with sodium at elevated temperatures[37a,b] or with sodium hydride[37c] gave **5a** in yields of 71%, 28%, and 30−40%, respectively.[37]

Likewise, the methyl ester of 2-phenylacetoxybenzoic acid gave **5d** on treatment with sodium (25%),[37b] dry potassium carbonate (85%),[37d] or potassium hydroxide in pyridine (40−60%).[37e] Coumarins **5b** and **5c** have not been prepared by cyclization involving 3−4 bond formation. The former has been obtained in 52% yield from 5-methyl-2-hydroxypropiophenone, dry potassium carbonate, and carbon dioxide (40 atm, 170 °C),[37f] and the latter in 4% yield from 1,4-dimethoxybenzene and methylmalonyl chloride catalyzed by aluminum chloride.[47]

Synthesis of 4-Hydroxyquinolin-2(1*H*)-ones. 4-Hydroxyquinolin-2(1*H*)-ones **13a**−**d** can be efficiently synthesized from the corresponding methyl *N*-(α-haloacyl)-anthranilates **12a**−**d** under similar cyclization conditions in the presence of sodium telluride (Scheme 6). Elimination to form a ketene is not a problem in this reaction because of the lower electronegativity of the nitrogen atom. This results in a higher yield of 4-hydroxy-1-methyl-3-phenylquinolinone **13c** (77%) as compared to 4-hydroxy-3-phenylcoumarin **5d** (10%). The synthesis of quinolinones has been reviewed,[48] and yields from other methods for formation of the 3−4 carbon−carbon bond in **13a**−**d** are as follows: **13a** (*N*-methylanthranilic acid,

SCHEME 6. Synthesis of 4-Hydroxyquinolin-2(1*H*)-ones



12a X=Br, R^1=H, R^2=Me
12b X=Br, R^1=R^2=Me
12c X=Cl, R^1=Ph, R^2=Me
12d X=Br, R^1=Me, R^2=Ph

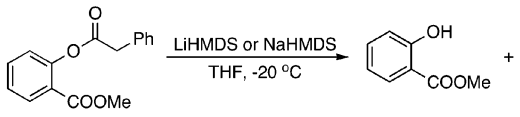
13a: yield 81%
13b: yield 55%
13c: yield 77%
13d: yield 88%

acetic anhydride, and/or acetic acid, 35−70%;[49] methyl *N*-acetyl-*N*-methylanthranilate, LDA, 54%;[50] 2-*N*-methylaminobenzaldehyde, ethyl chloroacetate, sodium hydride, 65%;[51] ethyl *N*-acetyl-*N*-methylanthranilate, sodium, xylene, 76%),[52] **13b** ([*N*-(2-bromopropionyl)-*N*-methyl-2-cyanoaniline, phenylmagnesium bromide, hydrolysis of imine, no yield given),[53] and **13c** (methyl ester of *N*-methyl-*N*-phenylacetylanthranilic acid and sodium ethoxide, 91%, or a basic ion-exchange resin, 86%).[54] Quinolinone **13d** apparently has not been prepared by cyclization to form the 3−4 bond,[55] but instead a cyclization involving heating of diphenylaniline and diethyl methylmalonate to form the 4−4a and 1−2 bonds has been reported in unspecified yield.[56]

Conclusions

A convenient synthesis of coumarins, 4-hydroxycoumarins, and 4-hydroxyquinolinones by a tellurium-triggered cyclization has been developed. The telluride method is advantageous in that it involves nonbasic conditions and avoids nonspecific proton removal that is troublesome in the Kostanecki−Robinson reaction. Enolates of esters are formed specifically from the α-haloester. Despite a few limitations, such as low yields of the 3-arylcoumarins and the necessity to use strictly anhydrous and nonprotic conditions to avoid protonation of the instantly formed enolate, the method offers some advantages: relatively cheap, nontoxic,[57] and recoverable

(45) Treatment of the methyl ester of 2-phenylacetoxybenzoic acid with sodium or lithium bis(trimethylsilyl)amide under conditions similar to the telluride cyclization gave methyl salicylate, phenylacetic acid, and a trace of coumarin **5d**:



This result indicates that a ketene elimination is not dependent on the presence of telluride, but depends only on the formation of the enolate.

(46) (a) Motoyoshiya, J.; Akinori, T.; Mikoshiba, R.; Yamamoto, I.; Gotoh, H. *J. Org. Chem.* **1980**, *45*, 5385−5387. (b) Fürstner, A.; Jumbarn, D. N.; Shi, N. *Z. Naturforsch. B*: *Chem. Sci.* **1995**, *50*, 326−331.

(47) Garden, J. F.; Hayes, N. F.; Thomson, R. H. *J. Chem. Soc.* **1956**, 3315−3318.

(48) Larsen, R. D. In *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations*; Bellus, D., Jacobsen, E. N., Ley, S. V., Noyori, R., Regitz, M., Schaumann, E., Shinkai, E., Thomas, E. J., Trost, B. M., Reider, P. J., Series Editors; Black, D. StC., Volume Editor; Thieme: Stuttgart, Germany, 2004; Vol. 15, pp 551−660.

(49) (a) Farbwerke vorm. Meister Lucius & Brüning in Hochst A. M., German Patent DE 287803, 1914. (b) Lutz, R. E.; Codington, J. F.; Rowlett, R. J.; Deinet, A. J.; Bailey, P. S. *J. Am. Chem. Soc.* **1946**, *68*, 1810−1812. (c) Kost, A. N.; Zhukauskaite, L. N.; Stankevichus, A. P. *Chem. Heterocycl. Compd.* (*N.Y., U.S.*) **1971**, *7*, 1141−1144. (d) Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1975**, *18*, 726−732. (e) Pandey, G.; Muralikrishna, C.; Bhalero, U. T. *Tetrahedron* **1989**, *45*, 6867−6874. (f) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642−3649. (g) Bratulescu, A. *J. Soc. Alger. Chim.* **2000**, *10*, 247−251; *Chem. Abstr.* **2001**, *135*, 242161.

(50) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790−5795.

(51) Apple, I. A.; Meth-Cohn, O. *ARKIVOC* **2002**, 4−14; *Chem. Abstr.* **2002**, *138*, 287337.

(52) Tomita, K. *Yakugaku Zasshi* **1951**, *71*, 1100−1112; *Chem. Abstr.* **1952**, *46*, 5044.

(53) Bergman, J.; Brynolf, A.; Vuorinen, E. *Tetrahedron* **1986**, *42*, 3689−3696.

(54) (a) Bezuglyi, P. A.; Ukrainets, I. V.; Treskach, V. I.; Turov, A. V. *Chem. Heterocycl. Compd.* (*N.Y., U.S.*) **1992**, *28*, 438−439. (b) Kulkarni, B. A.; Ganesan, A. *Chem. Commun.* (*Cambridge*) **1998**, 785−786.

(55) A patent claims a base-catalyzed Claisen condensation of esters of *N*-acyl-*N*-arylanthranilic acids.[56a]

(56) (a) Pfister, R.; Haefliger, F. U.S. Patent 3025299, March 13, 1962; *Chem. Abstr.* **1962**, *57*, 12444. (b) Kafka, S.; Klásek, A.; Kosmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394−6399.

(57) (a) Rules and Regulations. Environmental Protection Agency. In *U.S. Federal Register* **1996**, *61*, 20473−20490. (b) Lewis, R. J., Sr. *Sax's Dangerous Properties of Industrial Materials*; John Wiley: New York, 2000; Vol. 3, pp 3353−3354.

tellurium is used; no strong bases are required; formation of the enolates is fast, and the reactions proceed at room temperature or below; and the starting materials, α-halocarboxylic acids and *o*-hydroxy- or *o*-aminophenyl carboxylic esters, aldehydes, and ketones, are readily available. Atom economy is good in contrast to the ring-closing metathesis synthesis of coumarins.[38] In addition, this method may be applied to one-pot preparation of coumarins from the corresponding *o*-carbonylphenols as demonstrated by the synthesis of coumarin from salicylaldehyde.

Experimental Section

Preparation of Sodium Telluride.[58] A mixture of tellurium powder (200 mesh, 1.64 g, 12.8 mmol), sodium chips (0.604 g, 26.3 mmol), and naphthalene (0.336 g, 2.63 mmol) in anhydrous THF (12.8 mL) was refluxed under nitrogen for 48 h during which an off-white suspension of sodium telluride was formed. (The use of a stir bar is not recommended since the white Teflon stir bars become dark and the quality of the reagent appears to degrade within a few days.) The reaction flask was cooled to room temperature, and the approximately 1 M suspension is stored under nitrogen until used. The use of freshly prepared sodium telluride is recommended.

Generation of Lithium Telluride.[33,59] A solution of lithium triethylborohydride in THF (7.98 mL, 1 M, 7.98 mmol) was added to a suspension of tellurium powder (509 mg, 3.99 mmol) in THF (7.95 mL) at room temperature. The mixture was stirred for 4 h. Hydrogen evolved, and the color of the mixture gradually changed from black to pink and then to almost white. This 0.25 M "stock suspension" of finely divided lithium telluride in THF is stable for weeks at room temperature under an argon atmosphere and can be handled easily with an airtight syringe equipped with a stainless steel needle.

General Procedures for the Preparation of α-Haloesters and Amides: Procedure A. Pyridine or 2,6-lutidine (1.5 equiv) was added to a solution of a phenol or an aromatic amine (1 equiv) in CH_2Cl_2 followed by the corresponding α-haloacyl halide (1.2 equiv). The mixture was stirred at room temperature under argon (3−5 h) until TLC verified that the reaction was complete. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc, and the organic phase was dried (Na_2SO_4). The crude product was purified by flash chromatography (hexanes/EtOAc).

Procedure B. A modification of a literature method[60] was used. Salicylaldehyde (1 equiv) was added dropwise during 15 min at 0 °C to a suspension of sodium hydride (1.1 equiv) in THF (4 mL per 1 mmol of salicylaldehyde). The resulting pale yellow, viscous slurry was stirred for 2 h, and the α-bromoacyl bromide (1.2 equiv) was added dropwise over 10 min at 0 °C. After 25 min, the resulting white suspension of NaBr was removed by filtration; the solvent was evaporated, and the crude product was purified by flash chromatography (hexanes/EtOAc) to afford the α-bromoacylated salicylaldehydes, yields 90−98%.

General Procedures for the Preparation of Coumarins and Quinolinones: Procedure C. The solution of an α-haloester or amide (1 equiv) in THF (2 mL per 1 mmol of the substrate) was added to a suspension of sodium telluride (1 M in THF, 1.05 equiv) at −20 °C for coumarin preparation or at room temperature for quinolinone preparation. The mixture was stirred until TLC verified that the starting material was consumed. The tellurium precipitate was removed by centrifugation or filtration through a plug of Celite as previously described.[33,61] The solvent was evaporated, and aqueous KOH (5%) (for **3a**−**c**) or aqueous HCl (10%) (for **5a**−**d**, **13a**−**d**) was added. The aqueous solution was extracted with ether; the organic phase was dried (Na_2SO_4), and the solvent was removed to afford the crude product that was purified by flash chromatography (hexanes/EtOAc) or by crystallization.

Procedure D. Lithium telluride was used, and the procedure is described for the synthesis of coumarin **3a** (chromene-2-one). A "stock suspension" of lithium telluride (0.88 mL, 0.25 M, 0.22 mmol) was added to a solution of 2-(bromoacetoxy)-benzaldehyde **2a** (44 mg, 0.18 mmol) in THF (3 mL) at −78 °C. The mixture was stirred at this temperature for 1 h, warmed to room temperature, and stirred for an additional 30 min. Saturated aqueous $NaHCO_3$ (1 mL) and 30% aqueous H_2O_2 (1 mL) were added dropwise to oxidize triethylborane, and the mixture was stirred until gas ceased to evolve. (The tellurium powder is oxidized to water-soluble compounds.) The mixture was extracted with EtOAc (5 × 1 mL) and filtered through a pipet of Na_2SO_4. The crude product was purified by flash chromatography (hexanes/EtOAc) to afford coumarin **3a**[62] (20 mg, 0.14 mmol, 75%), mp 69−70 °C (lit.[62a] mp 67 °C (ethanol), lit.[62b] mp 71 °C (ethanol)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.5 Hz, 1 H), 7.55−7.45 (m, 2 H), 7.34−7.24 (m, 2 H), 6.41 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 154.4, 143.9, 132.3, 128.3, 124.8, 119.2, 117.3, 117.1.

Procedure E: One-Pot Preparation of Coumarin 3a. Salicylaldehyde (0.25 g, 2.0 mmol) was added dropwise during 15 min at 0 °C to a suspension of sodium hydride (0.053 g, 2.2 mmol) in THF (8.5 mL). The resulting pale yellow, viscous slurry was stirred for 2.5 h, and bromoacetyl bromide (0.57 g, 2.8 mmol) was added dropwise during 5 min at 0 °C. The mixture was stirred for 1 h at room temperature and cooled to −78 °C. A "stock suspension" of lithium telluride (12.2 mL, 0.25 M, 3.0 mmol) was added dropwise, and the resulting black suspension was stirred at this temperature for 1 h, warmed to room temperature, and stirred for an additional 30 min. Saturated aqueous $NaHCO_3$ (5 mL) and 5% aqueous H_2O_2 (15 mL) were added dropwise to oxidize triethylborane, and the mixture was stirred until gas ceased to evolve. The tellurium powder was oxidized to water-soluble compounds. The mixture was extracted with EtOAc (3 × 10 mL); the organic phase was dried (Na_2SO_4) and purified by flash chromatography (hexanes/EtOAc) to afford coumarin **3a** (0.16 g, 1.1 mmol, 55% from salicylaldehyde).

Trapping of Phenylketene Formed in the Reaction of 4d with Sodium Telluride. A suspension of sodium telluride (0.079 mL, 1 M in THF, 0.079 mmol) was added to the solution of **4d** (20 mg, 0.066 mmol) in THF (0.4 mL) at −78 °C. The mixture was stirred for 4 min, and benzylamine (21 mg, 0.20 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for an additional 40 min. The mixture was quenched with 5% HCl and extracted with EtOAc; the organic phase was dried (Na_2SO_4) and chromatographed (hexanes/EtOAc) to afford methyl salicylate (9 mg, 0.059 mmol, 90%) and *N*-benzyl phenylacetamide **11**[63a,b] (8.3 mg, 0.037 mmol, 56%), which was recrystallized from ethanol: mp 118−120 °C (lit.[63b] mp 118−120 °C).

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Supporting Information Available: General experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(58) Bhasin, K. K.; Gupta, V.; Gautam, A.; Sharma, R. P. *Synth. Commun.* **1990**, *20*, 2191−2195.
(59) Clive, D. L. J.; Anderson, P. C.; Moss, N.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1641−1647.
(60) Fuson, R. C.; Thomas, N. *J. Org. Chem.* **1953**, *18*, 1762−1766.
(61) Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Pepito, A. S.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 718−731.
(62) (a) Zwenger, C.; Dronke, F. *Justus Liebigs Ann. Chem.* **1862**, *123*, 145−157. (b) Meyer, H.; Beer, R.; Lasch, G. *Monatsh. Chem.* **1913**, *34*, 1665−1672.
(63) (a) Olah, G. A.; Narang, S. C.; Garcia-Luna, A. *Synthesis* **1980**, *8*, 661−662. (b) Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155−2162.